

Original article

Verinurad combined with febuxostat in Japanese adults with gout or asymptomatic hyperuricaemia: a phase 2a, open-label study

Masanari Shiramoto¹, Sha Liu², Zancong Shen², Xiaohong Yan², Amy Yamamoto², Michael Gillen³, Yasushi Ito⁴ and Jesse Hall²

Abstract

Objectives. Verinurad (RDEA3170) is a high-affinity inhibitor of the URAT1 transporter in clinical development for treating gout and asymptomatic hyperuricaemia. The aim of this Phase 2a, randomized, open-label study was to investigate the multiple-dose pharmacodynamics, pharmacokinetics and safety of oral verinurad combined with febuxostat vs febuxostat alone and verinurad alone.

Methods. Japanese male subjects aged 21–65 years with gout ($n=37$) or asymptomatic hyperuricaemia ($n=35$) and serum urate (sUA) ≥ 8 mg/dl were randomized to febuxostat (10, 20, 40 mg) in combination with verinurad (2.5–10 mg), verinurad alone (2.5–15 mg), febuxostat alone (10, 20, 40 mg) or benzbromarone alone (50 mg). There were four treatment periods per cohort and each treatment period was 7 days. Study drugs were administered once-daily after breakfast. Plasma, serum and urine samples were measured at pre-set intervals on days -1, 7, 14, 21 and 28.

Results. Verinurad combined with febuxostat decreased sUA in dose-dependent manner, providing greater sUA lowering than febuxostat alone at the same dose ($P < 0.001$). Urinary uric acid excretion rate was increased by verinurad, reduced by febuxostat and comparable to baseline for verinurad combined with febuxostat. Verinurad from 2.5 mg to 15 mg was well tolerated, with no withdrawals due to adverse events. Laboratory assessments showed no clinically meaningful changes during combination treatment.

Conclusion. Verinurad combined with febuxostat decreased sUA dose-dependently while maintaining uric acid excretion similar to baseline. All dose combinations of verinurad and febuxostat were generally well tolerated. These data support continued investigation of oral verinurad in patients with gout.

Trial registration. ClinicalTrials.gov, <https://clinicaltrials.gov>, NCT02317861

Key words: verinurad, febuxostat, pharmacokinetics, pharmacodynamics, serum urate, hyperuricemia, gout

Rheumatology key messages

- Verinurad is in clinical development for the treatment of gout and asymptomatic hyperuricaemia.
- Verinurad combined with febuxostat decreased serum urate dose-dependently in subjects with gout or asymptomatic hyperuricaemia.
- Verinurad and febuxostat dose combinations were generally well tolerated in subjects with gout or hyperuricaemia.

Introduction

Gout is an inflammatory arthritis characterized by the deposition of monosodium urate crystals in the joints, tendons

and other connective tissues, secondary to long-standing hyperuricaemia [1–3]. Hyperuricaemia itself is typically undetected until the symptoms of gout or its commonly associated comorbidities—including cardiovascular disease, chronic kidney disease and metabolic syndrome—are diagnosed [2, 4–6]. Successful management of gout requires a sustained reduction in the concentration of serum urate (sUA) below a target of <6.0 mg/dl, or <5.0 mg/dl in patients with severe gout symptoms, which leads over time to the dissolution of crystals, the alleviation of gout symptoms [7–9] and improved outcomes from cardiovascular, renal and other comorbidities [5].

¹SOUSEIKAI PS Clinic, Fukuoka, Japan, ²Ardea Biosciences, Inc., San Diego, CA, ³AstraZeneca LP, Gaithersburg, MD, USA and ⁴AstraZeneca K.K., Osaka, Japan

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Correspondence to: Masanari Shiramoto, Medical Corporation SOUSEIKAI PS Clinic, Random Square 8F, 6-18, Tenyamachi, Kakata-ku, Fukuoka-shi, Fukuoka 812-0025, Japan.
E-mail: masanari-shiramoto@ta-med.com

To achieve a sustained reduction in sUA, most patients require long-term urate-lowering therapy (ULT) [3]. Currently available ULTs include the xanthine oxidase inhibitors (XOIs) allopurinol and febuxostat, which reduce the production of urate, and the uricosurics probenecid, benzbromarone, sulfapyrazone and lesinurad, which increase the excretion of sUA by inhibiting its reabsorption [3]. Many patients fail to achieve their target sUA using an XOI as monotherapy [10, 11]. For these patients, management guidelines recommend combining ULTs with complementary mechanisms of action, such as an XOI with a uricosuric [9, 12, 13]. Japanese guidelines, in addition to providing guidance on the treatment of gout, offer recommendations on managing asymptomatic hyperuricaemia, on the basis that reducing sUA in these subjects can prevent the onset of gout [13]. The inclusion of a uricosuric in combination treatment represents a rational approach to managing this population, as inefficient renal excretion of uric acid contributes to elevated sUA in 85% of Japanese subjects with hyperuricaemia [14, 15].

The uricosuric lesinurad was recently approved in the USA and European Union in combination with an XOI for treating hyperuricaemia associated with gout in subjects not achieving target sUA with an XOI alone [16–18]. In the phase 3 clinical development programme, treatment with lesinurad 200 and 400 mg, in combination with febuxostat, resulted in more patients achieving target sUA and experiencing reduction in overall tophus area compared with febuxostat alone [17]. This treatment combination, however, showed only trends towards reductions in gout flares at 12 months at the highest dose tested (400 mg) [17], a dose that had increased renal adverse effects (compared with lesinurad 200 mg with febuxostat or febuxostat alone) and was neither submitted to, nor approved by, US and European regulatory agencies.

The clinical trial experience with ULTs has demonstrated that more precipitous and increasingly lowered sUA below target levels may lead to improved outcomes (e.g. lower gout flare incidence, more rapid tophus area reduction) [19–23].

Verinurad, a next-generation URAT1 inhibitor, demonstrates high potency in inhibiting URAT1 [24]. Verinurad doses as low as 2.5 mg produce significant sUA lowering in humans [25, 26], and this greater reduction in sUA may lead to improved outcomes and medical benefits for patients with gout. Verinurad in monotherapy studies has been associated with increased urinary uric acid concentrations and low rates of serum creatinine (sCr) elevation [25, 26]. Verinurad co-administered with an XOI has produced no cases of sCr elevation, which may be explained by the known inhibitory effects of XOIs on urate production [27–29]. The combination of verinurad with an XOI therefore has the potential to lower sUA to a greater extent than by XOIs alone, while reducing incidences of renal uric acid crystallization and sCr elevation.

This study evaluated the multiple-dose pharmacodynamics (PD), pharmacokinetics (PK) and safety of oral verinurad in combination with febuxostat compared with febuxostat alone or verinurad alone in Japanese male adults with gout or asymptomatic hyperuricaemia

(RDEA3170-205, NCT02317861). Febuxostat doses (10, 20 or 40 mg) were selected based on the initial recommended dose and most commonly prescribed maintenance doses in Japan. Benzbromarone (50 mg) was investigated as a reference URAT1 inhibitor [30].

Methods

Study design and subjects

Japanese male subjects with gout or hyperuricaemia and a screening sUA ≥ 8 mg/dl participated in this phase 2a, randomized, open-label, single-centre study. All subjects were aged 21–65 years with body weight ≥ 50 kg and BMI 18–40 kg/m². Gout was diagnosed by the treating physician from the subject's history and available laboratory data.

Six cohorts of subjects were randomized into treatment sequences to receive febuxostat (10, 20 or 40 mg) in combination with verinurad (dose range 2.5–10 mg), febuxostat alone (10, 20 or 40 mg), verinurad alone (dose range 2.5–15 mg) or benzbromarone alone (50 mg) (Fig. 1). There were four 7-day treatment periods per cohort and no washout periods between treatments, with the exception of cohort 6 (see Fig. 1). All study drugs were administered orally once daily in the morning after breakfast.

The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonisation/Good Clinical Practice and the Japanese Good Clinical Practice for Trials on Drugs (The Ministry of Health, Labour and Welfare Ordinance No. 28, 27 March 1997), partially revised by the Ministry of Health, Labour and Welfare Ordinance and their related notifications. The protocol, study and consent form were approved by an independent institutional review board (SOUSEIKAI Hakata Clinic). All subjects provided informed consent to participate in the study.

Blood and urine sampling

Serial plasma, serum and urine samples (total catch) were measured at frequent pre-set intervals on days -1, 7, 14, 21 and 28 for PD and PK assessments. On urine collection days, subjects were requested to drink 240 ml of water immediately after they rose in the morning (within 2 h pre-dose) in order to maintain urine output.

Analytical methods

Verinurad concentrations in plasma and urine and febuxostat concentrations in plasma were measured by Ardea Biosciences, Inc. (San Diego, CA, USA). Plasma samples were extracted by protein precipitation and analytes quantified by high-performance liquid chromatography–tandem mass spectrometry [31, 32]. Urine samples were prepared by dilution with water and quantified by high-performance liquid chromatography–tandem mass spectrometry. Detail on quantitative determination of benzbromarone and performance of the assays is provided in

Fig. 1 Study design

Group/ Period	Day 1–7	Day 8–14	Day 15–21	Day 22–28
Cohort 1	Febuxostat 10	Verinurad 2.5 + Febuxostat 10	Verinurad 2.5 + Febuxostat 20	Febuxostat 20
	Febuxostat 20	Verinurad 2.5 + Febuxostat 20	Verinurad 2.5 + Febuxostat 10	Febuxostat 10
Cohort 2	Febuxostat 10	Verinurad 5 + Febuxostat 10	Verinurad 5 + Febuxostat 20	Febuxostat 20
	Febuxostat 20	Verinurad 5 + Febuxostat 20	Verinurad 5 + Febuxostat 10	Febuxostat 10
Cohort 3	Febuxostat 20	Verinurad 5 + Febuxostat 20	Verinurad 5 + Febuxostat 40	Febuxostat 40
	Febuxostat 40	Verinurad 5 + Febuxostat 40	Verinurad 5 + Febuxostat 20	Febuxostat 20
Cohort 4	Febuxostat 20	Verinurad 10 + Febuxostat 20	Verinurad 10 + Febuxostat 40	Febuxostat 40
	Febuxostat 40	Verinurad 10 + Febuxostat 40	Verinurad 10 + Febuxostat 20	Febuxostat 20
Cohort 5	Verinurad 2.5	Verinurad 5	Verinurad 10	Verinurad 15
Cohort 6	Benzbromarone 50	Washout	Verinurad 2.5 + Febuxostat 10	Verinurad 5 + Febuxostat 20
	Verinurad 2.5 + Febuxostat 10	Verinurad 5 + Febuxostat 20	Washout	Benzbromarone 50

Doses are in milligrams.

supplementary data, section 'Assay methodology', available at *Rheumatology* online.

Endpoints and determinations

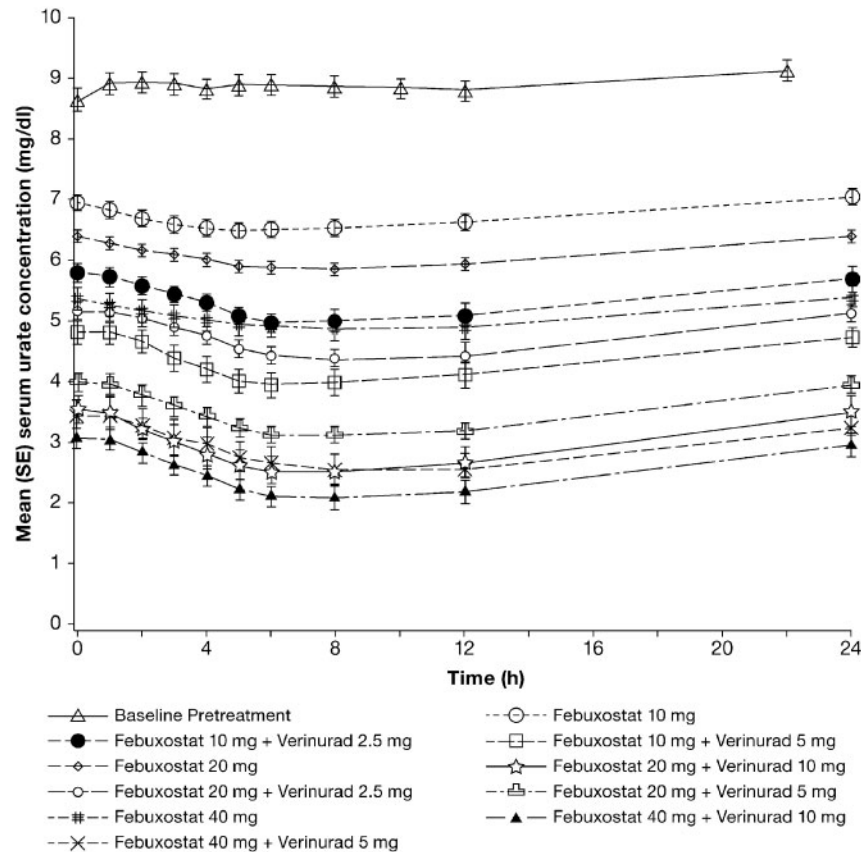
All subjects who received at least one dose of verinurad, febuxostat or benzbromarone and had evaluable PD data made up the PD population; all who received at least one dose of verinurad or febuxostat and had evaluable PK data made up the PK population; and all who received at least one dose of verinurad, febuxostat or benzbromarone constituted the safety population.

PD assessments included maximum percentage change and mean percentage change in sUA concentration from baseline on days 7, 14, 21 and 28; proportions of subjects with sUA ≤ 6.0 mg/dl at 4 h post-dose; rate of urinary uric acid excretion [Re_{UR} (mg/h)]; and fractional excretion of uric acid for each 24-h collection period [FEUA (%)]. For PD analyses, a mixed-effects model was used on E_{max} with treatment as a fixed effect, baseline concentration as a covariate and subject as a random effect separately for each cohort. Least squares means were calculated for each treatment group and the differences between treatment groups, together with 95% CI. Statistical testing of mean changes in sUA was conducted at an α level of 0.05;

the tests are included for descriptive purposes only, given this is an early phase study. No adjustments were made for multiple comparisons. PD analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

PK assessments for verinurad and febuxostat included area under the plasma concentration-time curve from time zero to 24 h post-dose (AUC_{0-24}), maximum observed plasma concentration (C_{max}), time to maximum observed plasma concentration (T_{max}) and plasma terminal half-life ($t_{1/2}$). The amount of verinurad excreted in urine over 24 h (Ae_{0-24}), percentage of unchanged verinurad in urine (fe_{0-24}) and renal clearance of verinurad (CL_{R0-24}) were also assessed. For PK analyses, a mixed-effects model was used to assess the impact of verinurad or febuxostat on AUC , C_{max} , Ae_{0-24} and CL_{R0-24} of the verinurad-febuxostat combination, with treatment as a fixed effect and subject as a random effect. Geometric mean squares (95% CI) are presented for verinurad alone or in combination with febuxostat 10, 20 or 40 mg, and for febuxostat alone or in combination with verinurad 2.5, 5 or 10 mg, together with geometric least squares mean ratios (90% CI). PK analyses were conducted by Ardea Biosciences, Inc., using Phoenix WinNonlin version 6.3 (Certara, Princeton, NJ, USA).

Subjects were monitored for safety throughout the study and at follow-up (day 42). Safety assessments included

Fig. 2 Mean (s.e.) serum urate concentrations (mg/dl): febuxostat alone or combined with verinurad

Pharmacodynamic analysis set, pooled cohort data.

adverse events (AEs) coded according to the Medical Dictionary for Regulatory Activities (version 18.0), clinical laboratory evaluations, vital signs, electrocardiograms and physical examinations. Any renal serious events were to be reviewed by an independent adjudication committee. Any haematology, chemistry or urinalysis abnormalities considered clinically relevant were to be assigned a severity rating by the investigator, based on Rheumatology Common Toxicity Criteria version 2.0 2007 [33]. Safety data are summarized by descriptive statistics using SAS version 9.3.

Results

Subjects

Seventy-two subjects with gout ($n = 37$) or asymptomatic hyperuricaemia ($n = 35$) were randomized to treatment sequences in each of the six cohorts. There were two treatment sequences for each cohort with six subjects in each treatment sequence. All subjects completed the study per protocol.

Demographic and other baseline characteristics of subjects grouped by cohort are summarized in Table 1. All subjects were males aged 21–65 years. Mean age, weight and BMI were similar between the cohorts. The mean

screening sUA ranged from 8.53 to 9.17 mg/dl across the cohorts.

Pharmacodynamics

sUA

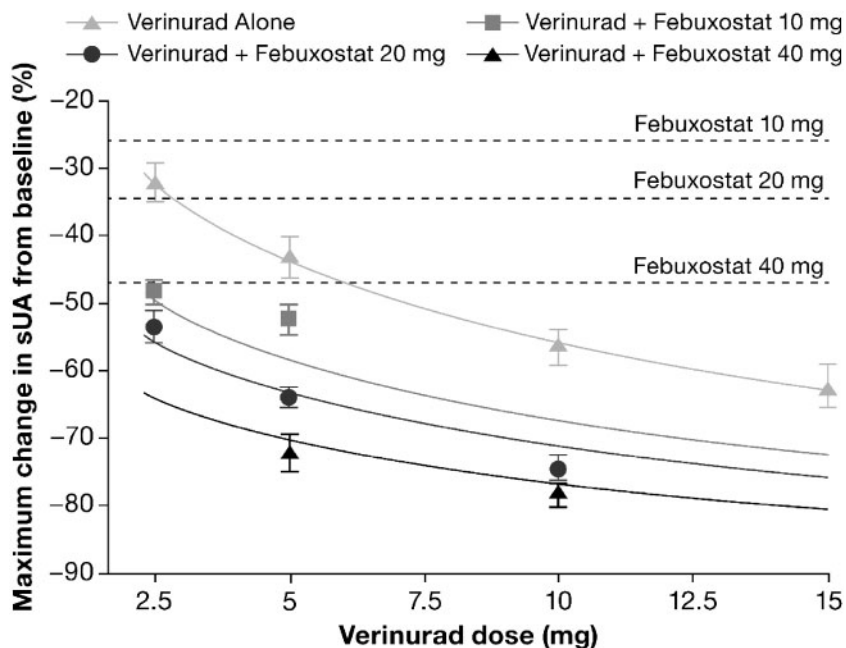
The time courses of mean sUA levels for febuxostat alone and for verinurad combined with febuxostat are shown in Fig. 2, demonstrating a downward trend in sUA for up to 12 h with each treatment. Both the mean changes in sUA (Fig. 2) and the maximum percentage changes in sUA (Fig. 3) were dose-dependent, and were greater for verinurad combined with febuxostat than for febuxostat alone. Percentage changes in sUA from baseline to 4 h post-dose are shown in supplementary Table S1, available at *Rheumatology* online, for the treatments in each cohort. All reductions in sUA from baseline to 4 h post-dose were significantly greater for verinurad combined with febuxostat than for febuxostat alone at the same dose or at the next higher febuxostat dose in each cohort ($P < 0.001$). Benzbromarone 50 mg was generally similar in sUA-lowering effect to verinurad 5 mg combined with febuxostat 20 mg (supplementary Fig. S1, available at *Rheumatology* online).

The proportions of subjects with sUA ≤ 6.0 mg/dl at 4 h post-dose are shown in supplementary Table S2,

TABLE 1 Demographic and other baseline characteristics

	Cohort 1 (n = 12)	Cohort 2 (n = 12)	Cohort 3 (n = 12)	Cohort 4 (n = 12)	Cohort 5 (n = 12)	Cohort 6 (n = 12)
Age, mean (s.d.), years	41.1 (10.6)	44.7 (16.2)	44.2 (8.2)	43.2 (9.8)	48.1 (12.8)	44.4 (13.8)
Body weight, mean (s.d.), kg	82.27 (14.14)	78.48 (16.84)	74.16 (8.62)	78.47 (11.8)	78.96 (10.94)	73.83 (6.05)
BMI, mean (s.d.), kg/m ²	28.1 (4.5)	27.5 (5.3)	24.9 (2.5)	27.1 (4.2)	27.4 (3.4)	25.2 (2.6)
Gout, n (%)	5 (41.7)	6 (50.0)	6 (50.0)	7 (58.3)	6 (50.0)	7 (58.3)
Asymptomatic hyperuricaemia, n (%)	7 (58.3)	6 (50.0)	6 (50.0)	5 (41.7)	6 (50.0)	5 (41.7)
sUA, screening, mean (s.d.), mg/dl	9.17 (1.09)	8.56 (0.60)	8.53 (0.74)	8.99 (0.95)	8.57 (0.61)	8.86 (0.85)
eGFR, mean (s.d.), ml/min	119 (19.7)	120 (32.2)	113 (19.7)	106 (23.8)	105 (24.0)	107 (22.2)

eGFR=[(140 – age) × ideal body weight (kg)]/[72 × serum creatinine (mg/dl)]. eGFR: estimated glomerular filtration rate based on serum creatinine, age and ideal body weight; sUA: serum urate.

FIG. 3 Mean (s.e.) Maximum percentage change in sUA: verinurad, febuxostat or verinurad combined with febuxostat

Solid lines are predictive trend lines based on additive changes from febuxostat and verinurad at various doses. Dashed horizontal lines represent the maximum change in sUA from baseline with febuxostat alone. Pharmacodynamic analysis set, pooled cohort data. sUA: serum urate.

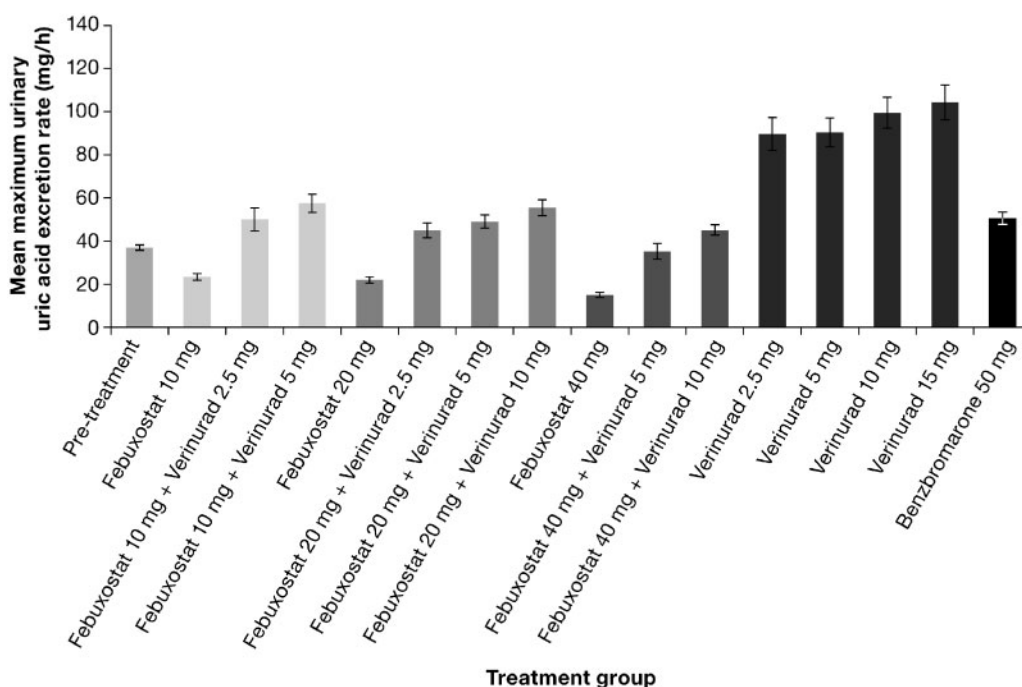
available at *Rheumatology* online. All subjects achieved sUA ≤ 6.0 mg/dl 4 h after treatment with verinurad 10 or 15 mg alone, benzbromarone 50 mg alone or verinurad in combination with febuxostat (with one exception in the verinurad 2.5 mg and febuxostat 10 mg group). At 4 h after treatment with febuxostat 10, 20 or 40 mg alone, sUA was ≤ 6.0 mg/dl in 20.8, 50.1 and 83.3%, respectively (pooled cohorts).

Urinary uric acid

Mean maximum Re_{UR} was increased by verinurad alone and reduced by febuxostat alone in a dose-dependent manner relative to baseline. For verinurad combined with febuxostat, the mean maximum Re_{UR} was similar to baseline and lower than or comparable to benzbromarone (Fig. 4).

FEUA was increased in a dose-dependent manner by verinurad alone and reduced by febuxostat alone relative

Fig. 4 Mean (S.E.) maximum urinary uric acid excretion rate (mg/h): verinurad, febuxostat or verinurad combined with febuxostat



Pharmacodynamic analysis set.

to baseline. For verinurad combined with febuxostat, FEUA was increased but to a lesser extent than for verinurad alone at the same dose (data not shown).

Pharmacokinetics

Median T_{max} of verinurad ranged from 3 to 4 h and mean $t_{1/2}$ from 13 to 24 h for varying verinurad doses alone or in combination with febuxostat (supplementary Table S3, available at *Rheumatology* online). The C_{max} and AUC_{0-24} of verinurad alone or in combination with febuxostat exhibited dose-related increases in the dose range investigated (Fig. 5 and supplementary Table S3, available at *Rheumatology* online). Plasma exposures of verinurad were generally comparable in the absence or presence of febuxostat, with geometric mean ratios ranging from 86.6 to 122% for C_{max} and 99.8 to 109% for AUC_{0-24} with varying doses of febuxostat. Similarly, plasma exposures of febuxostat were not consistently affected by varying doses of verinurad (supplementary Table S4, available at *Rheumatology* online).

The Ae_{0-24} of verinurad increased with increasing verinurad doses and febuxostat had no consistent effect (supplementary Table S3, available at *Rheumatology* online). fe_{0-24} was <2%. The CL_{R0-24} of verinurad ranged from 12.4 to 15.1 ml/min with verinurad alone and showed minimal change in the presence of febuxostat (data not shown).

Safety

Five subjects reported six treatment-emergent AEs (TEAEs) during treatment or follow-up (supplementary

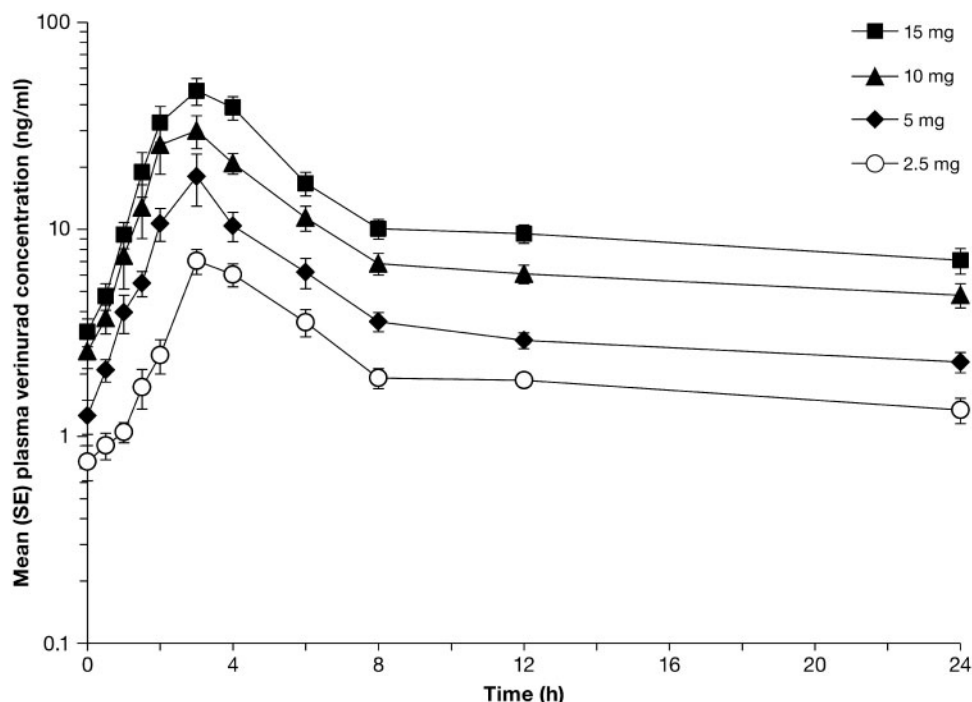
Table S5, available at *Rheumatology* online). The majority of TEAEs ($n=5$) were mild or moderate in severity and there were no serious AEs or withdrawals due to AEs during the study. Incidences of TEAEs were consistently low across the cohorts.

There were no clinically meaningful changes in clinical laboratory evaluations or vital signs in any cohort. Two subjects treated with verinurad 2.5 mg or verinurad 15 mg alone (cohort 5) showed a sCr elevation $\geq 1.5 \times$ baseline. In one of these subjects, sCr increased from 0.72 mg/dl at baseline to 1.12 mg/dl on day 2, and decreased to 0.91 mg/dl on day 8 and 0.76 mg/dl at follow-up. The second subject had a baseline sCr of 0.85 mg/dl that increased to 1.34 mg/dl on day 22 and decreased to 1.07 mg/dl at follow-up. There were no cases of sCr elevation in subjects treated with verinurad combined with febuxostat.

Discussion

Verinurad is a potent, selective inhibitor of the URAT1 transporter under clinical development to meet the current unmet needs in the chronic treatment of gout and asymptomatic hyperuricaemia. In this phase 2a, randomized, open-label study of 72 adult Japanese subjects with gout or hyperuricaemia, verinurad (dose range 2.5–10 mg) in combination with febuxostat (10, 20 or 40 mg) reduced sUA in a dose-dependent manner. Verinurad combined with febuxostat provided significantly greater decreases in sUA compared with febuxostat alone at the same

Fig. 5 Mean (S.E.) plasma concentrations of verinurad (ng/ml) following multiple once-daily oral administration of verinurad alone



Pharmacokinetic analysis set.

dose or at the higher febuxostat dose in each cohort. It is of note also that the proportion of subjects achieving sUA ≤ 6.0 mg/dl at 4 h post-dose was 91.7% at the lowest dose of verinurad (2.5 mg) combined with febuxostat (10 mg), compared with 83.3% for febuxostat 40 mg alone. These observations suggest that combining two treatments with different mechanisms of action can reduce sUA levels more consistently and lead to higher target achievement rates than a single agent alone at higher doses. Two other phase 2a studies investigating verinurad in combination with febuxostat or allopurinol, which were performed in Caucasian subjects with gout, also reported superior sUA lowering for the combination *versus* XO1 treatment alone [27, 28].

To fully characterize the rate of urinary uric acid excretion after verinurad treatment, urine samples were collected as frequently as hourly. We hypothesized that the peak rate of uric acid excretion may be a risk factor for development of acute urate nephropathy, while the 24-h elevation of uric acid excretion may be a risk factor for development of nephrolithiasis; nephrolithiasis is most likely to occur at night or in the early morning due to the low volume and relatively acidic pH of urine [34]. Consistent with the mechanism of action of verinurad via inhibition of URAT1, urinary uric acid excretion was increased by verinurad alone relative to baseline. Combining verinurad with febuxostat produced uric acid excretion levels similar to baseline and lower than or comparable to benzbromarone, a reference URAT1 inhibitor

that has not been associated with acute urate nephropathy. The risk of uric acid crystallization, manifesting as acute urate nephropathy or nephrolithiasis, may therefore be lessened by combining verinurad with febuxostat. There were no cases of sCr elevation in our study during combination treatment.

Verinurad plasma C_{max} and AUC exposures exhibited dose-proportional increases under steady-state conditions within the dose range investigated. Febuxostat did not affect the PK of verinurad, or vice versa, suggesting a lack of drug-drug interaction.

All dose combinations of verinurad and febuxostat were generally well tolerated, with no withdrawals due to AEs or serious AEs during study. Verinurad in combination with febuxostat was also associated with no clinical laboratory or vital sign abnormalities, consistent with an earlier drug-drug interaction study performed in volunteers [33].

Limitations of the study are its short study duration and the inclusion of only male subjects with gout. Strengths of the study include the investigation of subjects with gout or asymptomatic hyperuricaemia to provide clinical relevance, and the frequent blood and urine samplings that enhance the reliability of the PD and PK analyses. The frequent urine sampling in particular allowed detailed assessment of urinary uric acid excretion over time, which may be used to identify the dose combinations of verinurad and febuxostat that mitigate the risk of urinary over-excretion of uric acid.

In conclusion, the combination of verinurad with febuxostat in the dose ranges studied resulted in greater and more consistent sUA lowering than achieved by febuxostat alone in subjects with gout or asymptomatic hyperuricaemia. All dose combinations of verinurad and febuxostat were generally safe and well tolerated. These data in Japanese subjects support the continued development of verinurad with an XO1 as a novel dual-mechanism approach to treating patients with gout or asymptomatic hyperuricaemia.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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